Applicants respectfully traverse the rejection in view of the following comments.

Smith describes the cloning of SSAO and expression of full length, membrane-bound SSAO on the surface of Chinese hamster ovary (CHO) cells. Nowhere does Smith describe purification of this recombinant, non-soluble form of SSAO. In addition, Smith contains no description of a soluble form of SSAO.

The Advisory Action acknowledged that "Smith does not teach an isolated form of the enzyme" but asserted that "Smith does teach that the soluble form of SSAO lacks the membrane spanning portion of the wild-type SSAO." The Advisory Action cited Figure 1 and pages 20 and 21 of Smith in support of this assertion. Figure 1 of Smith contains, *inter alia*, a prediction that SSAO contains a transmembrane domain located between amino acid residues 5 and 27. However, applicants have carefully reviewed the passages of Smith identified in the Advisory Action and have been unable to find a reference to a soluble form of SSAO.

As detailed in the response to the previous Office Action, applicants submit that the claimed nucleic acids provide a solution to the long-felt but unsatisfied need of a means for purifying to homogeneity and in high amounts a recombinant human SSAO. The claimed nucleic acid permits the recombinant production of milligram quantities of pure, soluble, and biologically active human SSAO. Objective evidence that an invention fulfills a need that existed in the art for a long period of time without solution must be considered when assessing obviousness under 35 U.S.C. §103 (see, e.g., MPEP §716.04, I).

Smith describes recombinant expression of full length, membrane-bound SSAO on the surface of CHO cells. When performing enzyme assays intended to measure amine oxidase activity of the recombinant protein, Smith uses lysates from CHO cells expressing recombinant membrane-bound SSAO (see, e.g., Smith at page 18, right column). Smith describes the immunopurification of membrane-bound tissue-derived SSAO in quantities sufficient to obtain peptide sequences to assist in the cloning of the SSAO cDNA. However, Smith states that "[i]t was not possible to measure specific activities due to the very low yield of tonsillar VAP-1 protein obtained" (Smith at page 23, right column). Smith thus clearly states that its techniques

for purifying native, membrane-bound SSAO from tissue lysates were deficient in terms of the yield of protein obtained. As a result, Smith recognizes the need for a means of purifying high amounts of human SSAO.

As further evidence (i.e., in addition to the disclosure of Smith) of the long-felt but unsatisfied need of a means for purifying high amounts a recombinant human SSAO, Holt et al. (1998) *Biochemistry*, 37:4946-57 ("Holt") and Elmore et al. (2002) *J. Biol. Inorg. Chem.* 7:565-79 ("Elmore") both recognized the desirability of obtaining high yields and a homogeneous supply of a mammalian copper-containing amine oxidase such as SSAO (see, e.g., Holt in its Abstract stating "the identity of the quinone cofactor and the presence of copper remain unconfirmed, and SSAO has proved impossible to purify to homogeneity in sufficient yield to permit cofactor identification" (emphasis added); see also Elmore at page 567, left column, lines 8-18). In addition, Elmore (which was published approximately six years after the publication in 1996 of the cloning of human SSAO) noted that the heterologous overexpression and purification of recombinant human diamine oxidase described therein was "the first successful overexpression of any mammalian copper-containing amine oxidase"[1] (see Elmore in its Abstract and page 567, left column, lines 10-13; emphasis added).

The present application describes the successful expression and purification of a secreted fusion protein encoded by the claimed nucleic acid (see, e.g., page 15, line 20, to page 16, line 18). The fusion protein was secreted from mammalian cells transfected with the claimed nucleic acid and was purified directly from the culture medium by glutathione-affinity chromatography (see, e.g., page 16, lines 20-30). By specific proteolysis, the fusion partner (GST) and the protease were removed, providing a high yield (milligram quantities) of pure, soluble, and highly active recombinant human SSAO protein (see, e.g., page 17, line 1 to page 19, line 3), thereby satisfying the long-felt need recognized in the art.

[1] SSAO is a mammalian copper-containing amine oxidase.

The Advisory Action contained several assertions in response to applicants' argument that the claimed nucleic acids provide a solution to the long-felt but unsatisfied need for a means of purifying recombinant human SSAO to homogeneity and in high amounts. The following sections address these assertions in the order they were raised.

(i) The claims do not recite a limitation for a "means for purifying high amount of a recombinant soluble SSAO."

The Advisory Action responded to applicants' assertion that the invention provides a solution to a long-felt but unsatisfied need by stating that that "the claims do not recite said limitation that the nucleic acid permits for purifying a recombinant human soluble SSAO to homogeneity and in high amounts."

The pending claims are directed to nucleic acids that encode a recombinant human soluble SSAO. The claimed nucleic acids can be used to express the recombinant protein, which is subsequently purified to homogeneity and in high amounts. This intended use of the claimed nucleic acids is not and need not be included as a limitation of the composition claims. The properties and characteristics of a compound are inseparable from the compound itself. In re Papesch, 315 F.2d 381, 137 USPQ 43 (CCPA 1963). Applicants respectfully request that the Office cite authority for the proposition that a long felt need satisfied by a claimed composition needs to be included as a limitation of the claim.

(ii) Holt et al. (1998) *Biochemistry*, 37:4946-57

The Advisory Action stated that Holt does not provide "evidence of the long-felt but unsatisfied need of a means for purifying high amount of a recombinant soluble SSAO."

Holt states that "SSAO has proved impossible to purify to homogeneity in sufficient yield to permit cofactor identification" (Abstract). Holt clearly establishes both the need for purified SSAO (for the purpose of cofactor identification) and the failure of the art to achieve it (Holt states that SSAO has proved impossible to purify to homogeneity for this purpose). Holt's

inability to obtain purified SSAO underscores the need in the art for a means of purifying SSAO to homogeneity. The claimed nucleic acids meet that need.

(iii) Elmore et al. (2002) *J. Biol. Inorg. Chem.* 7:565-79

The Advisory Action stated that "the long-felt need has been satisfied by Elmore et al. before filing of the instant invention... Therefore, applicant's claim of a long-felt need for a long period of time without solution is invalid."

The present application claims priority to provisional application number 60/272,247, which was filed on February 28, 2001. All of the pending claims are entitled to the priority date of application number 60/272,247. The present application published as US20020160482 on October 31, 2002. Elmore states on page 565 that it was published online on February 13, 2002. Elmore was thus published after the filing of provisional application number 60/272,247 but before the publication of the present application. It was presumably because Elmore was unaware of applicants' prior unpublished patent application (which described success at preparing a soluble form of SSAO) that Elmore asserted that the heterologous overexpression and purification of recombinant human diamine oxidase described therein was "the first successful overexpression of any mammalian copper-containing amine oxidase" (Elmore at page 567, left column, lines 10-13 and Abstract). Contrary to the assertions in the Advisory Action, the long felt need was not satisfied by Elmore before the invention by applicants. Instead, Elmore's remarks reproduced in this and the previous response establish that the need was long-standing and that it was not satisfied before the present invention.

The objective evidence of record thus establishes that:

(i) there was a long-felt need in the art for a means of producing soluble recombinant human SSAO;

(ii) this long-felt need was not fulfilled prior to the filing of the present application; and

(iii) the present invention satisfies the long-felt need.

In view of the foregoing, applicants respectfully submit that the cited references do not render the claimed invention obvious and therefore request that the Examiner withdraw the rejection.

At pages 5-6 of the Advisory Action, claim 11 was rejected as allegedly unpatentable over Smith in view of Huston, Tudyka, and Zambidis et al. (1996) *Proc. Natl. Acad. Sci. USA* 93:5019-24 ("Zambidis"). Zambidis was cited only for its disclosure of a mouse IgG1 heavy chain signal peptide and thus does not cure the deficiencies in Smith, Huston, and Tudyka detailed above with respect to independent claim 1. As a result, the combination of references do not render obvious the nucleic acid of dependent claim 11.

At page 6 of the Advisory Action, claims 12, 13, 20, and 21 were rejected as allegedly unpatentable over Smith in view of Huston, Tudyka, and Brenda Enzyme Database, EC 3.4.22.28 ("Brenda"). Brenda was cited only for its disclosure of 3C protease amino acid sequences and thus does not cure the deficiencies in Smith, Huston, and Tudyka detailed above with respect to independent claim 1. As a result, the combination of references do not render obvious the nucleic acid of dependent claims 12, 13, 20, and 21.

CONCLUSIONS

Applicants ask that all claims be allowed in view of the amendments and remarks contained herein.

Enclosed is a Petition for Extension of Time and a check for the Petition for Extension of Time fee. Please apply any other charges or credits to deposit account 06-1050, referencing Attorney Docket No. 13425-053001.

Respectfully submitted,

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